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Antibiotic Exposure as a Risk Factor for Fluconazole-Resistant *Candida* Bloodstream Infection

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Recent exposure to azoles is an important risk factor for infection with fluconazole-resistant *Candida* spp., but little is known about the role of antibacterial drug exposure in the emergence of drug-resistant *Candida*. We did a prospective nationwide surveillance study of candidemia in Israel and analyzed the propensity score-adjusted association between antifungal and antibacterial drug exposure and bloodstream infection with *C. glabrata* and fluconazole-resistant *Candida* isolates. Four hundred forty-four episodes of candidemia (450 *Candida* isolates, 69 [15%] *C. glabrata* isolates, and 38 [8.5%] fluconazole-resistant isolates) from 18 medical centers in Israel were included. *C. glabrata* bloodstream infection was strongly associated with recent metronidazole exposure (odds ratio [OR], 3.2; $P < 0.001$). Infection with a fluconazole-resistant isolate was associated with exposure to carbapenems, trimethoprim-sulfamethoxazole, clindamycin, and colistin (odds ratio, 2.8; $P = 0.01$). The inclusion of antibacterial drug exposure in a multivariable model significantly enhanced the model's predictive accuracy for fluconazole-resistant *Candida* bloodstream infection. Our findings may be relevant to the selection of empirical antifungal treatment and broaden the scope of antibiotic-associated collateral damage.

Candida species have emerged as frequent causes of nosocomial bloodstream infection (BSI) in association with well-defined risk factors, including prolonged hospitalization, abdominal surgery, antibiotic treatment, neutropenia and central venous catheterization (14). Candidemia is associated with high rates of attributable mortality, prolongation of hospital stay, and excessive costs (28). In recent years, there has been a shift in the distribution of *Candida* species causing invasive infection, with non-*albicans* species now surpassing *Candida albicans* in many institutions (14, 25). Of particular concern is the rising incidence of the azole-nonsusceptible species *C. glabrata* and the inherently fluconazole-resistant species *C. krusei* (11, 25, 27).

Fluconazole is often used as empirical treatment of candidemia. However, given the correlation between the survival rate and the timely initiation of appropriate treatment for candidemia (8), accurate assessment of the risk of fluconazole-resistant *Candida* (FRC) BSI is of prime importance. Patients who were recently treated with an azole drug are at increased risk of infection with FRC (9) and should be treated initially with an echinocandin agent according to current guidelines (18). However, experimental and clinical data support the notion that nonantifungal antimicrobial agents also affect the risk of colonization and infection with FRC (15, 17, 22). Since exposure to antibacterial drugs among at-risk patients far exceeds exposure to antifungal agents, even modest effects of individual antibacterials could translate into significant overall changes in the susceptibility patterns of *Candida* spp. Nevertheless, the collateral effects of antibacterial drugs on *Candida* spp. are poorly understood. To address this question, we analyzed prospectively collected data from a nationwide study of candidemia in Israel and examined the association between exposure to antifungal and antibacterial agents and the risk of infection with FRC.

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MATERIALS AND METHODS

Study design. We performed a prospective nationwide study of candidemia in Israel from November 2005 through June 2007. Eighteen medical centers, which together account for 75% of the hospital beds in Israel, were included. All candidemia episodes that occurred in the participating centers during the study period were eligible for inclusion in this study. Clinical data were prospectively entered into standardized data forms by on-site investigators at each of the centers. The *Candida* sp. clinical isolates underwent preliminary identification and susceptibility testing in each center according to local practices. Subsequently, the isolates were transferred together with the corresponding data forms to the central study site, where species identification and susceptibility testing were performed as detailed below. The data forms were collected by the study coordinator, reviewed by the principal investigator, and entered into a computerized database. The study was approved by the ethics committee of each of the participating centers.

Data collection. On-site data collection included demographics, performance status, Charlson comorbidity index (4), and the presence of any of the following conditions in the month preceding candidemia: surgery, hematopoietic stem cell or solid-organ transplantation, cytotoxic chemotherapy, systemic corticosteroid treatment (a dose equivalent to predni-

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sone at ≥10 mg/day for at least 14 days), neutropenia (an absolute neutrophil count of <500 cells/μl), indwelling central vascular catheter, urinary bladder catheter, intravenous drug abuse, prematurity, intensive care unit hospitalization, mechanical ventilation, burns, or dialysis. In addition, a detailed history of antifungal and antibacterial drug use in the month preceding candidemia was obtained.

Microbiological testing. Species identification and susceptibility testing were performed at the central study site. All fungal isolates were maintained in sterile water at −80°C until testing. Prior to testing, each strain was passaged on Sabouraud's dextrose agar to ensure purity and viability. *Candida* species were identified using standard microbiology methods, including growth on Chromagar *Candida* (Chromagar, Paris, France) and the Vitek 2 system with use of the YST-ID card (bioMérieux, Durham, NC). Susceptibility to fluconazole was determined using the Etest (AB Biodisk, Sweden) method according to the manufacturer's instructions. Susceptibility results were interpreted according to the recently revised Clinical and Laboratory Standards Institute breakpoints for fluconazole (21). Specifically, for all *Candida* species except *C. glabrata* and *C. krusei*, fluconazole MIC breakpoints were as follows: susceptible, ≤2 μg/ml; susceptible dose-dependent, 4 to 8 μg/ml; and resistant, >8 μg/ml. For *C. glabrata*, the corresponding MIC breakpoints were <8 μg/ml, 16 to 32 μg/ml, and >32 μg/ml, respectively. *C. krusei* was considered always resistant to fluconazole. Susceptibility testing was performed at least in duplicate for each isolate, and the highest MIC was reported.

Statistical analyses. To identify predictors of FRC BSI, we first performed bivariable analyses using chi-square and Fisher's exact tests for categorical variables and Student's *t* test for continuous variables. The variables were then tested in a multivariable logistic regression model. The variables were added individually to the regression model to confirm their association with FRC BSI. Next, the simultaneous effects of variables that were significantly associated with FRC BSI individually were modeled. The significance threshold for retaining variables in the model was a *P* value of <0.05. Goodness of fit for multivariable models was assessed with the Hosmer Lameshow test, and predictive accuracy was assessed by calculating the area under the receiver-operator characteristics (ROC) curve.

The effect of antimicrobial drug exposure was analyzed for each drug separately, as well as for antimicrobial drug categories (β-lactams, penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, macrolides, tetracyclines, and triazoles) (see Table 2). Exposure to antibacterials with antianaerobic activity (metronidazole, clindamycin, carbapenems, β-lactam/β-lactamase inhibitor combinations, and chloramphenicol) was also analyzed in aggregate.

To limit confounding by nonantibacterial risk factors, we calculated the conditional probability of recent exposure to specific antibacterial drugs based on nonantibacterial risk factors using propensity score analysis (23, 24). Propensity scores were generated using logistic regression, with antibacterial drug exposure as the dependent variable. Nonantibacterial covariates were included in the multivariable model by stepwise selection, with a *P* value of <0.05 set as the limit for inclusion in the model. We tested whether the balancing property of the propensity score was satisfied by subclassification of the cohort into quintiles based on individual propensity scores. Then, using FRC BSI as the outcome variable, individual antibacterial drugs and drug classes were analyzed using logistic regression adjusted for the propensity score and the number of days at risk. Calculations were performed with the Stata software package (version 11.1; StataCorp, College Station, TX).

RESULTS

A total of 450 patient-specific *Candida* sp. bloodstream isolates from 444 patients were included in this study. Patient demographics and clinical risk factors for candidemia are summarized in Table 1. The majority of candidemia episodes (97.8%) were nosocomial; 355 (80%) occurred in hospitalized patients, and 79 (17.8%) occurred in outpatients discharged from the hospital within the previous 30 days and were therefore considered health care associated. *C. albicans* was the most frequent species (198 cases; 44.5%), followed by *C. parapsilosis* (*n* = 75; 16.8%), *C. tropicalis* (*n* = 74; 16.6%), and *C. glabrata* (*n* = 68; 15.3%).

TABLE 1 Demographic and clinical features of 444 patients with *Candida* bloodstream infection

Characteristic	Value[d]
Sex	
Male	238 (53.6)
Female	206 (46.4)
Age (yr)	65 (43–87)
≤1 yr	52 (11.7)
≥65 yr	224 (50.5)
Residence at a long-term care facility	48 (10.8)
Performance status	
Independent	191 (43.0)
Partially dependent	88 (19.8)
Completely dependent	89 (20.0)
Unknown	76 (17.1)
Charlson score	3 (1–5)
Exposure to candidemia risk factors[a]	
Antibiotic use	410 (92.3)
Central vascular catheter	331 (74.5)
Urinary bladder catheter	245 (55.1)
Parenteral nutritional support	147 (33.1)
Stay at an intensive-care unit	197 (44.4)
Mechanical ventilation	199 (44.8)
Surgery	175 (39.4)
Abdominal	87 (19.6)
Chest	26 (5.9)
Other	92 (20.7)
Cytotoxic chemotherapy	82 (18.5)
Neutropenia[b]	54 (12.2)
Dialysis	39 (8.7)
Prematurity	29 (6.5)
Stem cell transplantation	22 (5.0)
Burns	11 (2.5)
Systemic corticosteroids[c]	7 (1.6)
Intravenous drug abuse	7 (1.6)
Solid-organ transplantation	4 (0.9)
Severity of illness and outcome	
Shock	70 (15.7)
Renal failure	35 (7.8)
Respiratory failure	40 (9.0)
In-hospital death	216 (48.7)

[a] Within 30 days prior to the onset of candidemia.
[b] Absolute neutrophil count of <500 cells/μl.
[c] Defined as use of a systemic corticosteroid at a dose equivalent to prednisone at ≥10 mg/day for at least 14 days within the month preceding candidemia.
[d] All *n* (%), except age and Charlson score, which are median (interquartile range).

Antimicrobial drug exposure. Of 444 patients in the study cohort, 410 (92.3%) received treatment with at least one antibacterial agent within 30 days prior to the onset of candidemia. The most common antibacterial agents were β-lactams (88%), vancomycin (44%), aminoglycosides (31%), and metronidazole (29%)

TABLE 2 Unadjusted bivariate associations between antimicrobial drug exposure and *Candida* sp. infection in 444 patient-specific episodes of bloodstream infection

Antimicrobial agent	*n* (%)	*C. glabrata* (*n* = 68 [(15.3%])		Fluconazole-resistant *Candida* spp.[a] (*n* = 38 [8.5%])	
		Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
All antibacterial drugs[h]	410 (92)				
β-Lactam[b]	391 (88)	1.0 (0.4–2.6)	0.9	2.5 (0.6–22.7)	0.1
Penicillin[c]	262 (59)	0.9 (0.5–1.7)	0.8	1.7 (0.8–4.0)	0.1
β-Lactam/β-lactamase inhibitor[d]	200 (44)	0.8 (0.4–1.5)	0.6	1.4 (0.7–3.0)	0.2
Cephalosporin	240 (54)	1.0 (0.5–1.7)	0.8	**0.4 (0.1–0.8)**	**0.01**
Carbapenem	152 (34)	0.6 (0.3–1.1)	0.2	**2.3 (1.1–4.7)**	**0.01**
Fluoroquinolone	94 (21)	0.9 (0.4–1.8)	0.8	1.3 (0.5–3.0)	0.4
Metronidazole	130 (29)	**2.7 (1.5–4.7)**[i]	**<0.001**	1.2 (0.5–2.7)	0.4
Clindamycin	12 (2.7)	1.8 (0.5–6.6)	0.3	**3.7 (1.06–13.6)**	**0.03**
Trimethoprim-sulfamethoxazole	22 (4.9)	0.8 (0.1–3.0)	0.8	**4.5 (1.3–13.3)**	**0.001**
Macrolide	33 (7.4)	1.2 (0.4–3.2)	0.6	1.0 (0.1–3.7)	0.9
Vancomycin	196 (44)	0.6 (0.3–1.06)	0.06	1.2 (0.6–2.6)	0.4
Aminoglycoside	140 (31)	**0.4 (0.2–0.9)**	**0.01**	1.0 (0.4–2.1)	0.9
Colistin	31 (6.9)	1.0 (0.4–2.7)	0.8	**2.8 (1.1–7.2)**	**0.02**
Antianaerobic agents[e]	238 (53)	1.4 (0.6–2.5)	0.4	2.1 (0.8–6.3)	0.09
All antifungal drugs[f]	63 (14)	1.0 (0.4–2.2)	0.8	**4.8 (2.1–10.4)**	**<0.0001**
Amphotericin B	8 (1.8)	0.7 (0.01–6.2)	0.8	3.7 (0.3–21.6)	0.09
Fluconazole	56 (13)	1.2 (0.5–2.6)	0.6	**5.0 (2.2–11.0)**	**<0.0001**
Itraconazole	3 (0.7)	2.7 (0.04–54)	0.3	NA[g]	**<0.0001**
Voriconazole	3 (0.7)	0 (0–7.1)	0.4	5.4 (0.09–106.4)	0.1
Any triazole	61 (14)	1.1 (0.4–2.4)	0.7	**5.3 (2.4–11.6)**	**<0.0001**

[a] The fluconazole-resistant strains were *C. krusei* (*n* = 14), *C. parapsilosis* (*n* = 10), *C. glabrata* (*n* = 6), *C. tropicalis* (*n* = 5), *C. guilliermondii* (*n* = 2), and *C. farinosa* (*n* = 1) .
[b] Includes penicillins, cephalosporins, and carbapenems.
[c] Includes penicillin G, penicillin VK, amoxicillin, ampicillin, and cloxacillin.
[d] Includes amoxicillin-clavulanic acid, ampicillin-sulbactam, and piperacillin-tazobactam.
[e] Aggregate of antimicrobial agents with antianaerobic activity; includes metronidazole, clindamycin, carbapenems, and β-lactam/β-lactamase inhibitor combinations.
[f] There were no cases of candidemia in patients with exposure to echinocandins within the previous month.
[g] NA, not applicable, i.e., cannot be calculated because all 3 patients with itraconazole exposure had FRC BSI.
[h] Not shown in the table are antibacterial agents that were given to small numbers of patients: rifampin (8 patients), linezolid (6 patients), tetracyclines (5 patients), and nitrofurantoin (2 patients).
[i] Boldface indicates statistically significant associations.

(Table 2). Most patients (359; 81%) were exposed to multiple antibacterial drugs, either concomitantly or sequentially. Patients received a median of 3 antibacterial drugs (interquartile range, 2 to 4) in the month preceding candidemia. Sixty-three patients (14%) had received a systemic antifungal agent within 30 days prior to candidemia, most commonly fluconazole (56 patients) or amphotericin B (8 patients).

***C. glabrata* BSI.** There were 68 episodes of *C. glabrata* BSI. Bivariable analysis identified a positive association of *C. glabrata* infection with metronidazole exposure and a negative association with aminoglycoside exposure (Table 2). Nonantibiotic predictors of *C. glabrata* BSI were an age of ≥65 years, poor performance status, an indwelling urinary bladder catheter, residence at a long-term care facility, and a Charlson score of ≥1. Neutropenia and the presence of a central venous catheter were negatively associated with *C. glabrata* infection (Fig. 1A).

On multivariable analysis, recent metronidazole exposure remained a significant predictor of *C. glabrata* infection (adjusted odds ratio [OR], 3.2; 95% confidence interval [CI], 1.7 to 6.0; $P < 0.001$), together with poor performance status (OR, 1.8; $P = 0.04$), neutropenia (OR, 0.1; $P = 0.03$), and the presence of a central venous catheter (OR, 0.4; $P = 0.02$) (Fig. 1A).

Fluconazole-resistant *Candida* sp. BSI. Fifty-four episodes of candidemia (12.1%) were caused by isolates nonsusceptible to fluconazole: 16 (3.6%) were susceptible dose dependent, and 38 (8.5%) were resistant to fluconazole. The 38 fluconazole-resistant bloodstream isolates were *C. krusei* (14 of 14 isolates), *C. parapsilosis* (10/75; 13.3%), *C. glabrata* (6/68; 8.8%), *C. tropicalis* (5/74; 6.7%), *C. guilliermondii* (2/2), and *C. farinosa* (1/1).

Bivariable analysis revealed a significant association between FRC BSI and exposure to trimethoprim-sulfamethoxazole (TMP-SMX) (OR, 4.5; $P = 0.001$), carbapenems (OR, 2.3; $P = 0.01$), clindamycin (OR, 3.7; $P = 0.03$), and colistin (OR, 2.8; $P = 0.02$). Exposure to cephalosporins was negatively associated with FRC BSI (OR, 0.4; $P = 0.01$) (Table 2 and Fig. 1). Exposure to antianaerobic antibiotics was associated with a non-statistically significant trend for FRC BSI (OR, 2.1; $P = 0.09$).

As described in Materials and Methods, we constructed a propensity score that predicted a patient's likelihood of receiving any of the four antibacterial drugs associated with increased risk of FRC BSI. The nonantibacterial covariates ultimately included in the propensity score are shown in Table 3. Importantly, indices of the severity of illness at the time of candidemia (circulatory shock, renal failure, and respiratory failure) were not associated with the risk of exposure to one of these antibacterial agents. In the propensity-adjusted multivariable analysis, FRC BSI remained significantly associated with exposure to one of the four antibacterial

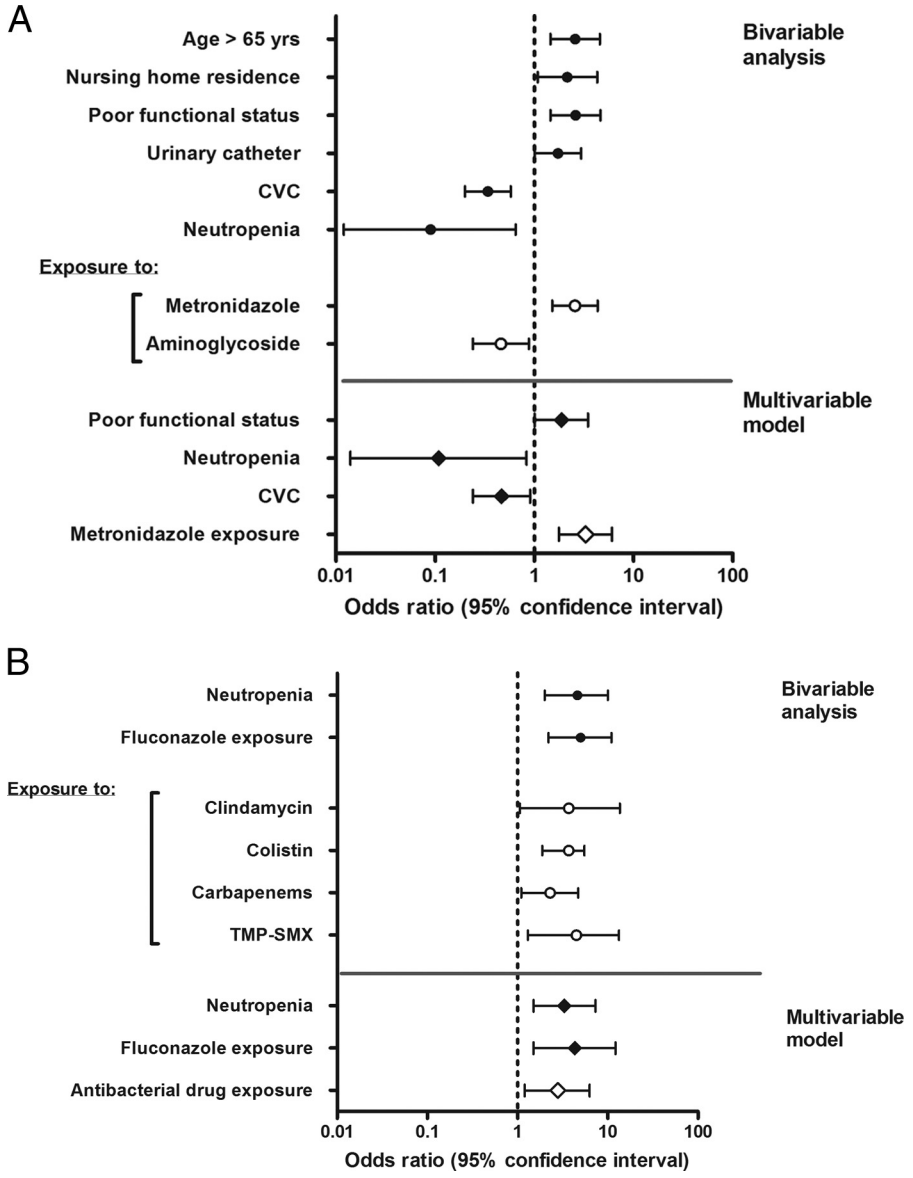

FIG 1 Association of antibiotic and nonantibiotic covariates with *C. glabrata*, and fluconazole-resistant *Candida* bloodstream infection. The forest plots show the associations of antibiotic and nonantibiotic covariates with *C. glabrata* BSI (A) and FRC BSI (B). The individual graphs show significantly associated covariates by bivariable analysis and multivariable analysis. The plots show the odds ratio (symbol) and 95% confidence interval (whiskers) for each covariate. Solid symbols are used for nonantibacterial covariates and open symbols for antibacterial covariates. All covariates refer to exposure within 30 days prior to the onset of candidemia. CVC, central venous catheter. Antibacterial drug exposure denotes exposure to carbapenems, trimethoprim-sulfamethoxazole, colistin, or clindamycin.

TABLE 3 Risk factors for exposure to a high-risk antibacterial drug[a] used to calculate the propensity score

Risk factor	Odds ratio (95% confidence interval)	*P* value
Urinary bladder catheter	2.2 (1.4–3.4)	<0.0001
Hematopoietic stem cell transplantation	3.6 (1.3–9.6)	0.009
Recent azole exposure	2.3 (1.2–4.3)	0.007
Time at risk	1.01 (1.008–1.02)	<0.0001

[a] High-risk antibacterial drugs were trimethoprim-sulfamethoxazole, carbapenems, clindamycin, and colistin.

drug classes (OR, 2.8; 95% CI, 1.2 to 6.3; $P = 0.01$), together with neutropenia (OR, 3.3; 95% CI, 1.5 to 7.3; $P = 0.002$) and recent fluconazole exposure (OR, 4.3; 95% CI, 1.5 to 12.2; $P = 0.005$) (Fig. 1).

To assess whether obtaining a history of recent antibacterial drug exposure can enhance the accuracy of predictive models to detect FRC BSI, we determined the incremental effect of antibacterial covariates on the area under the ROC curve. We compared the performances of three models; all included neutropenia as a covariate, together with previous fluconazole exposure (model 1), exposure to antibacterial drugs (carbapenems, trimethoprim-sulfamethoxazole, clindamycin, or colistin) (model 2), and exposure

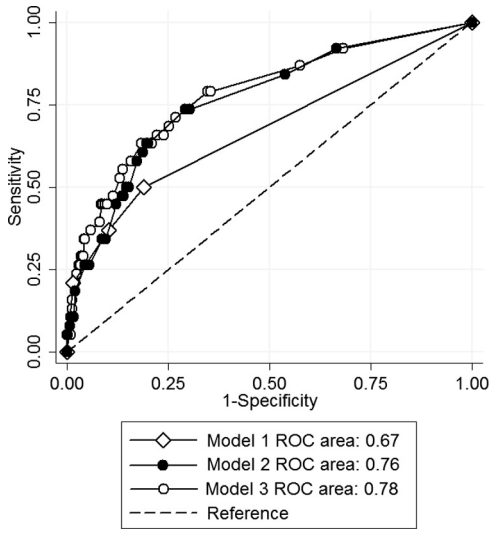

FIG 2 Comparative accuracy of predictive models for fluconazole-resistant *Candida* sp. bloodstream infection. The predictive accuracy, as represented by the area under the ROC plot, is shown for 3 models. FRC BSI is the dependent variable for all models. Covariates for model 1 were neutropenia and exposure to fluconazole; those for model 2 were neutropenia and exposure to antibacterial drugs (carbapenems, trimethoprim-sulfamethoxazole, clindamycin, or colistin); those for model 3 were neutropenia, exposure to fluconazole, and exposure to antibacterials. The area under the ROC curve was significantly higher for models that included antibacterial covariates (2 and 3) than for model 1 ($P = 0.003$).

to fluconazole and antibacterials (model 3). The predictive accuracy for FRC BSI, expressed as the area under the ROC curve, was 0.67, 0.76, and 0.78 for models 1, 2, and 3, respectively, and was significantly greater for models that included antibacterial exposure (models 2 and 3) than for the model that included only neutropenia and fluconazole exposure (model 1) ($P = 0.003$) (Fig. 2).

DISCUSSION

In this analysis of data from a national candidemia study, we found that recent exposure to antibacterial drugs affected the risk of bloodstream infection with fluconazole-resistant *Candida* isolates. Moreover, inclusion of antibacterial drugs in a multivariable model enhanced the model's predictive accuracy for fluconazole resistance compared to a model based on neutropenia and azole exposure alone. These findings suggest that "collateral damage," a term used to describe the adverse ecological effects of antibacterial drug use (19), extends beyond the selection of drug resistance among bacteria and that antibiotic pressure may have significant effects on azole resistance in *Candida* spp.

At least four potential mechanisms may underlie the observed associations between antibacterial drug exposure and candidemia. First, by altering the resident gut flora, antibacterials may selectively impair colonization resistance in a way that favors gastrointestinal colonization with drug-resistant *Candida* species. Colonization of the gut with *Candida* spp. is an antecedent to hematogenous dissemination in both immunocompetent and neutropenic individuals (5). Specifically, antibacterial drugs with predominant effects on anaerobic bacteria, such as metronidazole and clindamycin, were shown to promote intestinal colonization by *C. glabrata* in an animal model (22). In another study, the addition of metronidazole to a gastrointestinal decontamination regimen that included ciprofloxacin and fluconazole increased intestinal yeast colonization (26). Second, many antibacterial agents have some degree of antifungal activity (1), which could explain selective pressure similar to that induced by azole exposure. Metronidazole is an imidazole derivative with weak *in vitro* activity against *Candida* spp. but additive or synergistic fungicidal activity when combined with amphotericin B (3, 6). TMP-SMX and the polymyxins display *in vitro* activity against a variety of fungal organisms, including *Candida* spp. (2, 30). Third, some antibacterials directly modulate azole resistance by inducing the expression of efflux pump-encoding genes (13). Lastly, the immunomodulatory effects of antibacterial drugs might predispose for certain fungal pathogens. For example, sulfonamides were shown to have both inhibitory and stimulatory effects on the host response against *Candida* spp. (7, 16), whereas fluoroquinolones had no effect at therapeutic concentrations (10).

A number of case-control studies have reported exposure to antibacterial drugs with an antianaerobic spectrum of activity as a risk factor for candidemia (29), and more specifically for *C. glabrata* BSI (15, 17). Similar to our findings, Lee at al. reported that metronidazole use was associated with fluconazole-susceptible *C. glabrata* BSI, but not with fluconazole-resistant *C. glabrata* BSI (15). Interestingly, 3 of the 5 antibacterial drugs linked with fluconazole-resistant isolates in our study (metronidazole, clindamycin, and carbapenems) have significant antianaerobic activity.

A striking feature of the current cohort of patients with candidemia is the almost universal exposure to antibacterial drugs in the preceding month. Moreover, the majority of patients received multiple classes of antibacterials, either concomitantly or sequentially. These findings underscore the importance of addressing the antibacterial burden, which in a hospitalized population frequently constitutes the sum of multiple drug effects.

The limitations of our study are inherent in its observational nature. Exposure to antibacterial drugs may reflect several confounding covariates, such as severity of illness, length of hospitalization, and comorbid conditions (confounding by indication). In our patient cohort, there was no significant association between the occurrence of FRC BSI or exposure to the antibacterials of interest and severity of illness. We sought to adjust for possible confounders using multivariable analyses and propensity score adjustment. Propensity score matching aims to balance confounding covariates between antibiotic-treated and untreated patients. Importantly, we adjusted all risk estimates for the number of days at risk. However, even this methodology cannot correct for unknown confounders. In addition, it should be noted that the rate of fluconazole resistance in *C. glabrata* isolates was lower than that reported for most populations (20). Different antibacterial drugs may affect fluconazole resistance in populations where higher *C. glabrata* resistance rates are observed. Thus, our predictive model should be validated for different patient cohorts. Of note, we used the recently adjusted CLSI clinical breakpoints for fluconazole and *Candida* susceptibility, which should increase the sensitivity of detecting emerging resistance in common *Candida* sp. isolates (21). Compared with previous CLSI breakpoints, use of the current values increased the rate of fluconazole resistance in *Candida* bloodstream isolates from 5.3% to 8.5%, with the most marked increase occurring in *C. parapsilosis* (1.3% to 13.3%).

Unnecessary use of antibiotics is frequent, accounting for as much as 30% of total antimicrobial therapy days, with antianaerobic agents accounting for a third of redundant antibacterial drug

use (12). It is now well recognized that antibacterial drugs promote the emergence and dissemination of multidrug-resistant nosocomial bacteria in a class-specific manner (19). Selection of fluconazole-resistant invasive *Candida* strains may represent an additional adverse consequence of excessive antibiotic use. Recognizing robust associations between antibacterial drug exposure and FRC BSI should allow the implementation of improved predictive schemes to direct empirical antifungal treatment in high-risk patients.

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